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<b>14. ABSTRACT</b> This study determined the effectiveness of 6 days (d) of staging at 2200m on physiologic adjustments and acute mountain sickness (AMS) during rapid, high-risk ascent to 4300m. Eleven sea-level (SL) resident men (means +SD; 21+3 yr; 78+13 kg) completed resting measures of end-tidal CO <sub>2</sub> (Petco <sub>2</sub> ), arterial oxygen saturation (Sao <sub>2</sub> ), heart rate (HR), and mean arterial pressure (MAP) at SL and within 1 h of exposure to 4300m in a hypobaric chamber prior to 6 d of staging at 2200m (preSTG) and on the summit of Pikes Peak following 6 d of staging at 2200m (postSTG). Immediately following resting ventilation measures, all performed submaximal exercise (~55% of altitude-specific maximal oxygen uptake) for ~2 h on a bicycle ergometer to induce higher levels of AMS. AMS-C, calculated from the Environmental Symptoms Questionnaire, was measured following 4 h and 8 h of exposure at preSTG and postSTG, and the mean was calculated. Resting Petco <sub>2</sub> (mmHg) was unchanged from SL (39.8+2.6) to preSTG (39.3 +3.0), but decreased ( p<0.05) from preSTG to postSTG (32.8+2.6). Resting Sao <sub>2</sub> (%) decreased ( p<0.05) from SL (97+2) to preSTG (80+4) and increased ( p<0.05) from preSTG to postSTG (83+3). Resting HR (bpm) and MAP (mmHg) did not change in					
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# Effect of Six Days of Staging on Physiologic Adjustments and Acute Mountain Sickness during Ascent to 4300 Meters

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## Abstract

Beidleman, Beth A., Charles S. Fulco, Stephen R. Muza, Paul R. Rock, Janet E. Staab, Vincent A. Forte, Michael D. Brothers, and Allen Cymerman. Effect of six days of staging on physiological adjustments and acute mountain sickness during ascent to 4300 meters. *High Alt. Med. Biol.* 10:253–260, 2009.—This study determined the effectiveness of 6 days (d) of staging at 2200 m on physiologic adjustments and acute mountain sickness (AMS) during rapid, high-risk ascent to 4300 m. Eleven sea-level (SL) resident men (means  $\pm$  SD;  $21 \pm 3$  yr;  $78 \pm 13$  kg) completed resting measures of end-tidal CO<sub>2</sub> (PETCO<sub>2</sub>), arterial oxygen saturation (Sao<sub>2</sub>), heart rate (HR), and mean arterial pressure (MAP) at SL and within 1 h of exposure to 4300 m in a hypobaric chamber prior to 6 d of staging at 2200 m (preSTG) and on the summit of Pikes Peak following 6 d of staging at 2200 m (postSTG). Immediately following resting ventilation measures, all performed submaximal exercise ( $\sim 55\%$  of altitude-specific maximal oxygen uptake) for  $\sim 2$  h on a bicycle ergometer to induce higher levels of AMS. AMS-C, calculated from the Environmental Symptoms Questionnaire, was measured following 4 h and 8 h of exposure at preSTG and postSTG, and the mean was calculated. Resting PETCO<sub>2</sub> (mmHg) was unchanged from SL ( $39.8 \pm 2.6$ ) to preSTG ( $39.3 \pm 3.0$ ), but decreased ( $p < 0.05$ ) from preSTG to postSTG ( $32.8 \pm 2.6$ ). Resting Sao<sub>2</sub> (%) decreased ( $p < 0.05$ ) from SL ( $97 \pm 2$ ) to preSTG ( $80 \pm 4$ ) and increased ( $p < 0.05$ ) from preSTG to postSTG ( $83 \pm 3$ ). Resting HR (bpm) and MAP (mmHg) did not change in any of the test conditions. The incidence and severity of AMS-C decreased ( $p < 0.05$ ) from preSTG ( $91 \pm 30\%$ ;  $1.05 \pm 0.56$ ) to postSTG ( $45 \pm 53\%$ ;  $0.59 \pm 0.43$ ), respectively. These results suggest that modest physiologic adjustments induced by staging for 6 d at 2200 m reduced the incidence and severity of AMS during rapid, high-risk ascent to 4300 m.

**Key Words:** hypobaric hypoxia; arterial oxygen saturation; resting ventilation; heart rate; mean arterial pressure

## Introduction

**S**TAGING OR TEMPORARILY RESIDING at a moderate altitude for several days prior to ascending to a higher altitude has long been used as a practical altitude-acclimatization strategy to reduce the incidence and severity of acute mountain sickness (AMS) (Malconian and Rock, 1988; Roach et al., 2001). The basic premise of staging is that physiologic adjustments (e.g., increase in ventilation, decrease in plasma volume) induced by exposure to a moderate altitude (e.g., 2200 m) will carry over to a higher elevation and thereby reduce the adverse consequences of direct, rapid ascent to high altitude (Richalet et al., 1992). Several studies have reported that staging for 4 d or more at a moderate altitude reduced AMS by

25% to 85% during the first few days at a higher altitude (Hansen et al., 1967; Evans et al., 1976; Stamper et al., 1980; Muza et al., 2000).

Previous staging studies, however, did not assess AMS utilizing a high-risk scenario involving physical exercise, which is known to increase the incidence of AMS (Roach et al., 2000). Thus, the number of staging days needed to significantly reduce AMS utilizing a rapid, high-risk ascent to altitude may be underestimated in previous studies. In addition, previous studies did not assess AMS using validated questionnaires such as the Environmental Symptoms Questionnaire (ESQ) (Sampson et al., 1994) or the Lake Louise AMS Scoring System (LLS) (Roach et al., 1993). Further, none of the previous studies systematically and quantitatively assessed

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physiologic adjustments before and after staging to determine whether beneficial physiologic adjustments induced by staging at a moderate altitude are associated with observed decrements in AMS following ascent to high altitude. Finally, most of these prior studies assessed AMS before and after staging, but provided no information about physiologic adjustments and AMS symptoms during the staging period.

From a practical viewpoint, the staging altitude should be high enough to induce beneficial physiologic adaptations, but low enough such that sleep is not disturbed, illness is not induced, and performance can be maintained. In addition, the staging altitude should be easily accessible, exist in many parts of the country, and provide habitable living conditions for large numbers of people to be effective and useful. Previous research has demonstrated that altitudes between 2000 and 2500 m are well tolerated by most people, and people living at these altitudes demonstrate modest degrees of altitude acclimatization (Boning et al., 2001; Schmidt et al., 2002; Muza et al., 2004; Brothers et al., 2007). Therefore, an altitude of 2200 m was selected as an easily accessible, practical, and potentially useful staging altitude for this study.

The purpose of this study was to assess the effect of 6 d of staging at 2200 m on physiologic adjustments and the incidence and severity of AMS following rapid, high-risk ascent to 4300 m. We hypothesized that 6 d of staging at 2200 m would be well tolerated, yet induce modest ventilatory and hematologic acclimatization such that both the incidence and severity of AMS would be greatly reduced following rapid, high-risk ascent to 4300 m.

## Methods

### Study volunteers

Eleven healthy male lowlanders with a baseline age (mean  $\pm$  SD;  $21 \pm 3$  yr), height ( $177 \pm 7$  cm), and weight ( $78 \pm 13$  kg) completed this study. Each was a lifelong low-altitude resident and had no exposure to altitudes greater than 1500 m for at least 2 months immediately preceding the start of SL baseline testing in this study. All volunteers received a medical examination, and none had any condition warranting exclu-

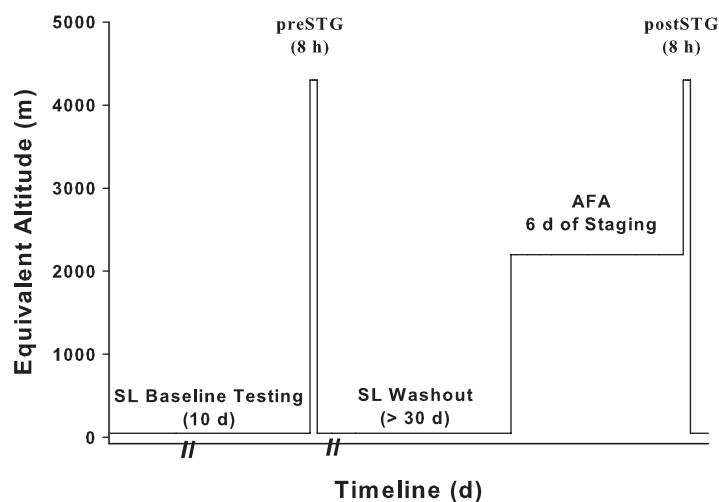
sion from the study. All tested within normal ranges for pulmonary function, hemoglobin concentration, and serum ferritin levels. Nine were nonsmokers and two smoked 10 or less cigarettes per day. Each gave verbal and written acknowledgment of his informed consent and was made aware of his right to withdraw without prejudice at any time. The study was approved by the Institutional Review Board of the U.S. Army Research Institute of Environmental Medicine in Natick, Massachusetts, USA. Investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

### Study design

The study utilized a prospective, unblinded crossover design. The test conditions were defined as sea-level (SL) baseline testing (10 d) and washout ( $> 30$  d), exposure to 4300 m in a hypobaric chamber prior to staging (preSTG) (8 h), and exposure to 4300 m on the summit of Pikes Peak following 6 d of staging at 2200 m (postSTG) (8 h). In addition, measurements were also made at the U.S. Air Force Academy in Colorado Springs, Colorado, USA (2200 m) after 24 h of exposure (STG24), 72 h of exposure (STG72), and 120 h of exposure (STG120). A minimum 30-d washout period at SL existed between preSTG and STG24 such that the staging intervention could be evaluated apart from the effects of a previous altitude exposure (Schneider et al., 2002). An outline of the study design and testing schedule is shown in Fig. 1.

### Ventilatory and cardiovascular assessment

Body weight (BW) was measured in T-shirts and shorts immediately prior to measurements of resting ventilation. Resting ventilation was then measured in the morning after a 2-h fast and approximately following 1-h exposure in all test conditions. Volunteers sat in a semirecumbent position and breathed through a low-resistance breathing circuit connected to a breath-by-breath, open-circuit metabolic system (Vmax 229, Sensormedics, Inc., Yorba Linda, CA, USA) calibrated with certified gases and volume standard. Each volunteer's



**FIG. 1.** This study utilized a repeated-measures design on 11 male volunteers with test condition as the repeated factor. The test conditions were defined as sea level (SL) for baseline testing (10 d) and washout (30 d) during exposure to 4300 m in a hypobaric chamber prior to 6 d of staging at 2200 m (preSTG) and during exposure to 4300 m on the summit of Pikes Peak following 6 d of staging at the U.S. Air Force Academy (AFA) at 2200 m (postSTG).

resting minute ventilation ( $\dot{V}_E$ ), end-tidal oxygen, carbon dioxide partial pressure ( $P_{ET}O_2$  and  $P_{ET}CO_2$ ) were measured. Simultaneously, arterial oxygen saturation ( $SaO_2$ ) and heart rate (HR) were measured by pulse oximetry (Nonin Model 8600, Plymouth, MN). Ventilation data were collected for 10 min, and the mean over the last 5 to 8 min of the session was calculated. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a manual sphygmomanometer after completing ventilatory measures. Mean arterial pressure was calculated as  $0.333(SBP - DBP) + DBP$ .

#### Hematologic assessment

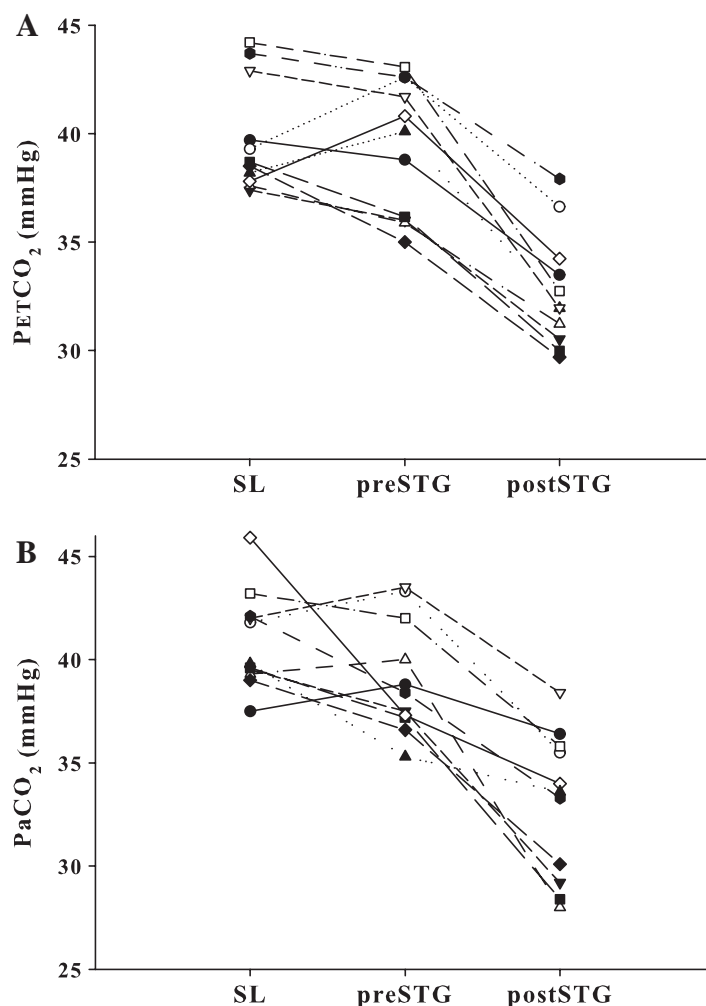
Immediately following the resting ventilation measurements, blood samples were obtained. Anaerobic samples of capillary-arterialized blood were obtained from the fingertip after warming the hand in  $43^\circ C$  water for 5 min. The partial pressure of arterial carbon dioxide ( $P_{a}CO_2$ ), inverse log of the  $H^+$  ion concentration (pH), and bicarbonate ion concentration ( $HCO_3^-$ ) were measured in these samples. Additionally,

venous blood samples were obtained from the forearm without stasis for the measurement of hemoglobin concentration [Hb] and hematocrit (Hct). Percent change in plasma

volume (PV) from SL values at preSTG and postSTG was calculated according to the Dill equation (Dill and Costill, 1974). The arterialized and venous blood samples were analyzed immediately in duplicate using an iStat portable clinical analyzer (Abbott Diagnostics, Abbott Park, IL, USA). Blood gas measurements were not collected during the 6 d of staging at 2200 m, and venous blood measurements were made only at STG24 and STG120.

#### Altitude-illness assessment

Approximately 10 min after the blood samples, all volunteers performed a submaximal exercise bout for  $\sim 2$  h on a bicycle ergometer ( $\sim 55\%$  of altitude-specific maximal oxygen uptake) to induce higher levels of AMS (Roach et al., 2000). AMS was assessed at approximately 4 h and 8 h into each test condition. The incidence and severity of AMS were determined from information gathered using the ESQ (Sampson et al., 1994) and the LLS (Roach et al., 1993). The shortened electronic version of the ESQ, which is a self-reported 11-question inventory, was used to quantify a weighted AMS cerebral factor score (AMS-C) (Beidleman et al., 2007). The mean AMS-C score was calculated from two time points (4 h and 8 h), and AMS was judged to be present if an individual's



**FIG. 2.** Individual changes in the partial pressure of end-tidal carbon dioxide ( $P_{ET}CO_2$ ) and capillary-arterialized  $P_{CO_2}$  at sea level (SL), within 1 h of exposure to 4300 m in a hypobaric chamber prior to 6 d of staging at 2200 m (preSTG) and within 1 h of exposure to 4300 m on the summit of Pikes Peak following 6 d of staging at 2200 m (postSTG).

AMS-C score was  $\geq 0.7$  at any time point (Sampson et al., 1994). The LLS consists of a 5-question, self-reported assessment of AMS symptoms, and the mean of the two time points (4 h and 8 h) was calculated (Roach et al., 1993). Total LLS scores that include headache and are  $\geq 3$  (range, 0 to 15) at any time point were diagnostic of AMS.

#### Environmental conditions

All SL and preSTG testing was performed in a hypobaric or climatically controlled chamber maintained at a temperature and relative humidity of  $21 \pm 2^\circ\text{C}$  and  $45 \pm 5\%$ , respectively. The SL testing was performed at ambient barometric pressure ( $\sim 760$  mmHg), and preSTG testing was conducted at an altitude equivalent to 4056 m ( $P_B = 459$  mmHg), which was equivalent to the terrestrial altitude of 4300 m on the summit of Pikes Peak. The staging testing (STG24, STG72, and STG120) was performed at 2200 m ( $P_B = 601$  mmHg) in a climatically controlled room at the U.S. Air Force Academy maintained at a temperature and relative humidity of  $22 \pm 2^\circ\text{C}$  and  $45 \pm 5\%$ , respectively. The postSTG testing was conducted on the summit of Pikes Peak at an altitude of 4300 m ( $P_B = 458$  to 462 mmHg). Indoor temperature and humidity of the Pikes Peak laboratory were  $20 \pm 2^\circ\text{C}$  and  $40 \pm 5\%$ , respectively.

#### Statistical analyses

For all measurements, a one-way, repeated measures ANOVA was used to analyze differences between the test conditions (SL, preSTG, and postSTG) and staging conditions (STG24, STG72, and STG120) using Statistica v11.0 (Statsoft, Tulsa, OK, USA). Significant main effects and interactions were analyzed using Tukey's least significant difference test. Pearson product-moment correlations were calculated for the relationships between individual changes in AMS and individual changes in ventilatory, cardiovascular, and hematologic parameters from preSTG to postSTG. It was estimated that a sample of 9 volunteers would provide a  $>80\%$  chance of detecting a 5-mmHg decrease in  $PETCO_2$  or  $Paco_2$ , our primary measures of altitude acclimatization, given a 4-mmHg standard deviation. For all tests, statistical significance was set at  $p < 0.05$ . Data are presented as means  $\pm$  SE.

## Results

#### Resting ventilatory measures of acclimatization

Eight of the eleven volunteers demonstrated a decrease in  $PETCO_2$  and  $Paco_2$  (i.e., increase in ventilation) from SL to preSTG. Eleven volunteers demonstrated a further decrease in  $PETCO_2$  and  $Paco_2$  from preSTG to postSTG (Fig. 2). The mean values for resting ventilatory measures of acclimatization in all test conditions are presented in Table 1. The  $PETCO_2$  and  $Paco_2$  did not change from SL to preSTG, but decreased  $\sim 17\%$  from preSTG to postSTG (Table 1). Pulmonary gas exchange, as measured by  $Sao_2$  was improved  $\sim 3\%$  from preSTG to postSTG. The  $HCO_3^-$  decreased, but pH remained the same from preSTG to postSTG. There was no correlation between individual changes in AMS-C and any measure of ventilatory acclimatization from preSTG to postSTG.

#### Resting cardiovascular measures of acclimatization

There was no change in HR (bpm) from SL ( $69 \pm 6$ ) to preSTG ( $70 \pm 6$ ) to postSTG ( $65 \pm 6$ ). There was also no change

TABLE 1. RESTING VENTILATORY INDEXES OF ACCLIMATIZATION IN EACH OF THE TEST CONDITIONS

	SL (50 m)	preSTG (4300 m)	postSTG (4300 m)
$PETCO_2$ (mmHg)	$39.8 \pm 2.6$	$39.3 \pm 3.0$	$32.7 \pm 2.6^{a,b}$
$PETO_2$ (mmHg)	$104.6 \pm 5.0$	$47.6 \pm 2.3^a$	$50.2 \pm 3.0^{a,b}$
E (L/min)	$10.9 \pm 2.2$	$12.6 \pm 2.3$	$13.4 \pm 2.7$
$O_2$ (mL/min)	$375 \pm 62$	$384 \pm 61$	$310 \pm 55^{a,b}$
$CO_2$ (mL/min)	$330 \pm 76$	$359 \pm 66$	$274 \pm 46^b$
E/ $O_2$	$29.1 \pm 2.8$	$32.8 \pm 2.0^a$	$42.9 \pm 3.9^{a,b}$
E/ $CO_2$	$33.3 \pm 2.0$	$35.2 \pm 3.0$	$48.6 \pm 4.0^{a,b}$
RER	$0.87 \pm 0.09$	$0.93 \pm 0.09$	$0.87 \pm 0.08$
$Sao_2$ (%)	$97 \pm 2$	$80 \pm 4.0^a$	$83 \pm 3^{a,b}$
$Paco_2$ (mmHg)	$40.9 \pm 2.3$	$38.5 \pm 3.3$	$32.4 \pm 3.0^{a,b}$
pH	$7.41 \pm 0.03$	$7.44 \pm 0.03$	$7.46 \pm 0.03^a$
$HCO_3^-$ (mM)	$25.8 \pm 1.0$	$26.1 \pm 1.3$	$23.1 \pm 1.3^{a,b}$

Values are mean  $\pm$  SD; SL, sea level; preSTG, during acute ( $\sim 1$  h) exposure to 4300-m altitude-equivalent prior to 6 d of staging at 2200 m; postSTG, during acute ( $\sim 1$  h) exposure to 4300 m on the summit of Pikes Peak following 6 d of staging at 2200 m;  $PETCO_2$ , partial pressure of end-tidal carbon dioxide;  $PETO_2$ , partial pressure of end-tidal oxygen; E, minute ventilation;  $O_2$ , oxygen consumption;  $CO_2$ , carbon dioxide production; E/ $O_2$ , ventilatory equivalent for oxygen; E/ $CO_2$ , ventilatory equivalent for carbon dioxide; RER, respiratory exchange quotient;  $Sao_2$ , arterial oxygen saturation;  $Paco_2$ , partial pressure of capillary-arterialized carbon dioxide; pH, capillary-arterialized inverse log of the  $H^+$  ion concentration;  $HCO_3^-$ , capillary-arterialized bicarbonate concentration. <sup>a</sup> $p < 0.05$  from SL; <sup>b</sup> $p < 0.05$  from preSTG.

in SBP or DBP from SL ( $120 \pm 7$ ;  $79 \pm 10$  mmHg) to preSTG ( $114 \pm 7$ ;  $75 \pm 10$  mmHg) or postSTG ( $116 \pm 10$ ;  $76 \pm 7$  mmHg). MAP did not change from SL ( $92 \pm 8$  mmHg) to preSTG ( $88 \pm 8$  mmHg) to postSTG ( $89 \pm 6$  mmHg).

#### Resting hematologic measures of acclimatization

There was no change in [Hb] or Hct from SL to preSTG, but both increased from preSTG to postSTG (Table 2). The %PV reduction from SL values also increased from preSTG to postSTG. BW (kg) did not change from SL ( $78 \pm 13$ ) to preSTG ( $79 \pm 13$ ), but decreased from preSTG to postSTG ( $77 \pm 13$ ). There were no correlations between individual changes in AMS-C and any of the hematologic or BW measures from preSTG to postSTG.

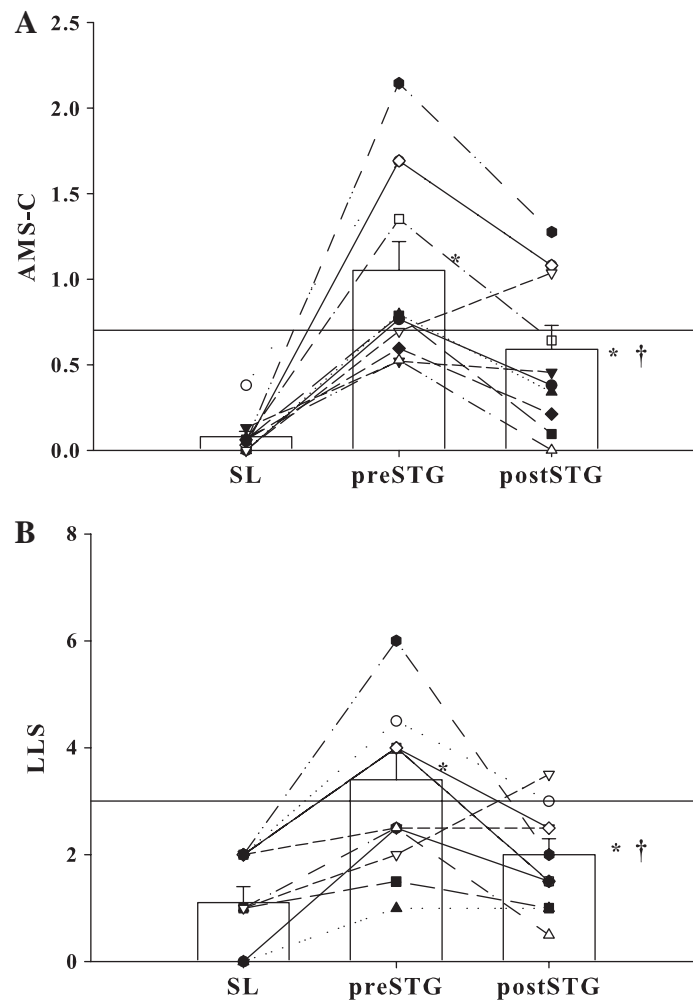
#### Altitude-illness measures

Figure 3 demonstrates individual and group changes in the severity of AMS as measured by both the ESQ and LLS from

TABLE 2. RESTING HEMATOLOGIC INDICES OF ACCLIMATIZATION IN EACH OF THE TEST CONDITIONS

	SL (50 m)	preSTG (4,300 m)	postSTG (4,300 m)
[Hb] (g $\cdot$ dl $^{-1}$ )	$14.6 \pm 0.7$	$14.8 \pm 0.9$	$15.3 \pm 0.7^{*,\dagger}$
Hct (%)	$43.1 \pm 5.3$	$43.5 \pm 3.3$	$45.1 \pm 3.9^{*,\dagger}$
PV reduction (%)		$1.3 \pm 6.9$	$7.4 \pm 7.9^\dagger$

Values are mean  $\pm$  SE; SL, sea level; preSTG, during acute ( $\sim 1$  h) exposure to 4,300 m altitude-equivalent prior to 6 d of staging at 2,200 m; postSTG, during acute ( $\sim 1$  h) exposure to 4,300 m on the summit of Pikes Peak following 6 d of staging at 2,200 m; [Hb], venous hemoglobin concentration, Hct, venous hematocrit; PV, plasma volume; <sup>\*</sup> $P < 0.05$  from SL, <sup>†</sup> $P < 0.05$  from preSTG.



**FIG. 3.** Individual and group changes in acute mountain sickness cerebral factor score (AMS-C) calculated from the Environmental Symptoms Questionnaire (ESQ) and Lake Louise AMS Scoring System (LLS) self-report score at sea level (SL) during exposure to 4300 m in a hypobaric chamber prior to 6 d of staging at 2200 m (preSTG) and during exposure to 4300 m on the summit of Pikes Peak following 6 d of staging at 2200 m (postSTG). The reference lines of 0.7 for the ESQ and 0.3 for the LLS represent the cutoff scores for classification of AMS. \* $p < 0.05$  from SL; † $p < 0.05$  from preSTG.

SL to preSTG to postSTG. Both the ESQ and LLS demonstrated an increase in the severity of AMS from SL to preSTG followed by an  $\sim 44\%$  mean reduction in the severity of AMS from preSTG to postSTG (Fig. 3). In addition, the ESQ demonstrated an  $\sim 46\%$  reduction in the incidence of AMS from preSTG ( $91 \pm 30\%$ ) to postSTG ( $45 \pm 53\%$ ), while the LLS demonstrated an  $\sim 18\%$  change in the incidence of AMS from preSTG ( $72 \pm 46\%$ ) to postSTG ( $54 \pm 50\%$ ). There was a significant correlation between individual changes in AMS-C and MAP from preSTG to postSTG ( $r = 0.85$ ;  $p = 0.002$ ) (Fig. 4).

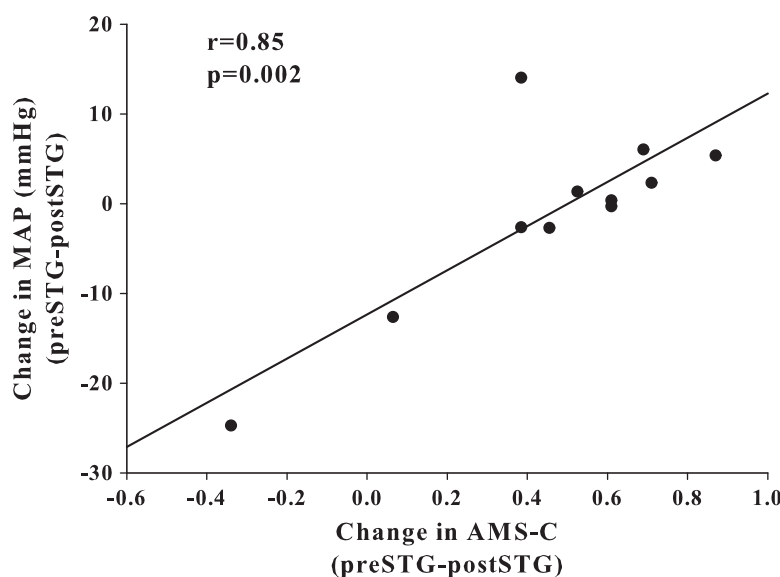
#### *Physiologic measures and altitude illness during staging*

Table 3 demonstrates ventilatory, cardiovascular, and hematologic indexes of acclimatization during the 6 d of staging at 2200 m. None of the physiologic parameters changed from STG24 to STG120. As expected, both the mean AMS-C and LLS scores at STG24 ( $0.14 \pm 0.26$ ;  $0.70 \pm 1.9$ ), STG72 ( $0.04 \pm 0.09$ ;  $0.20 \pm 0.66$ ), and STG120 ( $0.03 \pm 0.09$ ;  $0.10 \pm 0.33$ ) were well below the AMS-criterion scores of 0.7 and 3 for each

questionnaire, respectively. The incidence of AMS at STG 24 was  $9 \pm 30\%$  and  $27 \pm 46\%$  as determined by the ESQ and LLS, respectively. At STG72 and STG120, neither the ESQ nor LLS detected any incidence of AMS.

#### **Discussion**

This is the first study to demonstrate that modest physiologic adjustments induced by 6 d of staging at 2200 m resulted in great reductions in the incidence and severity of AMS during rapid, high-risk ascent to 4300 m. Although the ventilatory, cardiovascular, and hematologic adjustments at the staging altitude (Table 3) were relatively minor, these adjustments ultimately conferred significant benefits during ascent to a higher altitude. In addition, 6 d of staging at 2200 m was well tolerated by the majority of individuals, with a very low incidence of AMS (9% to 25%) reported only in the first 24 h of exposure to 2200 m. Within an individual, the magnitude of change in the severity of AMS-C from preSTG to postSTG was not related to the magnitude of ventilatory and hematologic acclimatization, but was significantly related to changes in MAP.



**FIG. 4.** Correlation between individual changes (preSTG – postSTG) in acute mountain sickness cerebral factor score (AMS-C) and mean arterial pressure (MAP) during exposure to 4300 m in a hypobaric chamber prior to 6 d of staging at 2200 m (preSTG) to exposure to 4300 m on the summit of Pikes Peak following 6 d of staging at 2200 m (postSTG).

All ventilatory measures, including both metabolic parameters and blood gas values, indicated that 6 d of staging at 2200 m induced ventilatory acclimatization. Resting ventilation, as measured by  $\text{PETCO}_2$  and  $\text{Paco}_2$ , was increased ~17% from preSTG to postSTG, which compares favorably with the 16% increase reported during an acute exposure to 4300 m

**TABLE 3.** RESTING VENTILATORY, HEMATOLOGIC, AND CARDIOVASCULAR INDEXES OF ACCLIMATIZATION DURING SIX DAYS OF STAGING AT 2200 M

	STG24 (2200 m)	STG72 (2200 m)	STG120 (2200 m)
$\text{PETCO}_2$ (mmHg)	$36.2 \pm 1.7$	$35.7 \pm 2.3$	$35.0 \pm 2.0$
$\text{PEtO}_2$ (mmHg)	$74.2 \pm 3.3$	$73.8 \pm 2.7$	$74.1 \pm 1.7$
E (L/min)	$11.7 \pm 1.7$	$11.0 \pm 1.6$	$11.1 \pm 1.2$
$\text{O}_2$ (mL/min)	$366 \pm 40$	$332 \pm 37^a$	$335 \pm 43^a$
$\text{CO}_2$ (mL/min)	$320 \pm 43$	$288 \pm 40$	$280 \pm 36^a$
E/ $\text{O}_2$	$31.8 \pm 2.3$	$33.3 \pm 3.6$	$33.3 \pm 3.5$
E/ $\text{CO}_2$	$36.6 \pm 1.9$	$38.6 \pm 4.4$	$39.8 \pm 4.3^a$
RER	$0.87 \pm 0.04$	$0.86 \pm 0.04$	$0.84 \pm 0.05$
Sao <sub>2</sub> (%)	$94 \pm 1$	$93 \pm 2$	$94 \pm 2$
[Hb] (g/dL <sup>-1</sup> )	$14.7 \pm 0.9$		$15.0 \pm 0.9$
Hct (%)	$43.3 \pm 1.7$		$44.0 \pm 2.9$
HR (bpm)	$68 \pm 10$	$67 \pm 10$	$66 \pm 3$
SBP (mmHg)	$118 \pm 13$	$117 \pm 10$	$111 \pm 10$
DBP (mmHg)	$77 \pm 10$	$80 \pm 7$	$79 \pm 7$
MAP (mmHg)	$91 \pm 10$	$92 \pm 7$	$90 \pm 7$

Values are mean  $\pm$  SE; SL, sea level; preSTG, during acute (~1 h) exposure to 4300-m altitude-equivalent prior to 6 d of staging at 2200 m; postSTG, during acute (~1 h) exposure to 4300-m altitude on the summit of Pikes Peak following 6 d of staging at 2200 m;  $\text{PETCO}_2$ , partial pressure of end-tidal carbon dioxide;  $\text{PEtO}_2$ , partial pressure of end-tidal oxygen; E, minute ventilation;  $\text{O}_2$ , oxygen consumption;  $\text{CO}_2$ , carbon dioxide production; E/ $\text{O}_2$ , ventilatory equivalent for oxygen; E/ $\text{CO}_2$ , ventilatory equivalent for carbon dioxide; RER, respiratory exchange quotient; Sao<sub>2</sub>, arterial oxygen saturation; [Hb], venous hemoglobin concentration; Hct, venous hematocrit; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

following 4 d of staging and acetazolamide use at 1600 m (Evans et al., 1976). We had expected our values for capillary-arterialized  $\text{PCO}_2$  to be higher than values for  $\text{PETCO}_2$  in all test conditions. Short exposure of the capillary-arterialized sample to air may have caused a decrease in  $\text{PCO}_2$  values. Although this is a possibility, all samples were collected by the same technicians using the utmost care in capping and immediately analyzing the samples in all test conditions. In addition, the direction of change in both  $\text{PCO}_2$  and  $\text{PETCO}_2$  from preSTG to postSTG consistently reflects that ventilatory acclimatization occurred following 6 d of staging at 2200 m.

The blood gas measurements ( $\text{Paco}_2$ ,  $\text{HCO}_3^-$ , and pH) also indicated a respiratory alkalosis due to hyperventilation that was partially compensated for by increased excretion of  $\text{HCO}_3^-$  to maintain a normal pH following staging. Only one study has reported a 6% increase in resting ventilation, as measured by capillary-arterialized  $\text{PCO}_2$ , in volunteers exposed to a gradual ascent to altitude (4 d at 2150 to 3500 m) versus a control group (Purkayastha et al., 1995). The final exposure altitude in that study, however, was low (3500 m) and as such would result in a smaller increase in ventilation. Further, the additional 2 d of staging in the present study compared to the other study (Purkayastha et al., 1995) may confer some additional ventilatory acclimatization benefits.

Pulmonary gas exchange was also improved during acute exposure to 4300 m following 6 d of staging at 2200 m. The 3% increase in Sao<sub>2</sub> from preSTG to postSTG (Table 1) was larger than the 1% increase previously reported by our laboratory following 4 d of staging at 2000 m (Muza et al., 2000). Again, in the present study, the additional 2 d of staging may be responsible for the greater magnitude of improvement in pulmonary gas exchange. Although staging for 6 d at 2200 m induced only half of the ventilatory acclimatization observed following 2 to 3 weeks of altitude residence at 4300 m (7% to 8% increase in Sao<sub>2</sub>) (Reeves et al., 1993), staging appears to represent a viable means for reducing the hypoxic stress associated with acute exposure to high altitude during the time course when symptoms of AMS are most likely to appear.



Although there was no association between individual changes in AMS-C scores and any of the ventilatory measures in the present study, previous acclimatization studies suggest that ventilatory acclimatization plays a role in reducing the severity of AMS (Beidleman et al., 2004; Muza et al., 2004; Burtcher et al., 2008).

Six days of staging at 2200 m induced hematologic acclimatization as evidenced by the ~5% increase in [Hb] and Hct from preSTG to postSTG (Table 2). Most likely, this increase in Hct was due to the ~7% reduction in PV from preSTG to postSTG. Similar to our results for ventilatory acclimatization, the magnitude of hematologic acclimatization was about half of that observed following 2 to 3 weeks of altitude residence at 4300 m (i.e., 10% to 20% reduction in PV) (Beidleman et al., 1997; Sawka et al., 2000). The magnitude of change in [Hb] in the present study, however, was similar to the 3.4% difference reported between gradual ascent and control volunteers during an acute exposure to 3500 m (Purkayastha et al., 1995). Although an increase in [Hb] will contribute to an increase in arterial O<sub>2</sub> content, the relative contribution from such a small change in [Hb] to overall O<sub>2</sub> delivery would be relatively minor and have little impact on the development of AMS (Sawka et al., 2000). The decrease in PV, however, from preSTG to postSTG is likely of greater importance because people who do not develop high altitude diuresis often show increased symptoms of AMS (Swenson et al., 1995; Hoyt and Honig, 1996; Ledderhos et al., 2002). As such, it was surprising that individual changes in AMS-C and %PV reduction from preSTG to postSTG were not significantly correlated.

Staging did not appear to induce typical cardiovascular adjustments associated with altitude acclimatization such as a decrease in resting HR and increase in MAP (Wolfel and Levine, 2001). HR tended to decrease ( $p = 0.07$ ) from preSTG ( $70 \pm 2$ ) to postSTG ( $65 \pm 4$ ), but values did not reach significance. The magnitude of decrease in HR (5 bpm) in the present study, however, was similar to the results reported from a previous study comparing gradual ascent and acute induction to altitude (Purkayastha et al., 1995). Although a few studies have reported that signs of exaggerated (Loeppky et al., 2003) or decreased (Fulco et al., 1989) sympathetic activation are associated with increased and decreased AMS, respectively, the relationship between a reduction in HR and AMS is not well established. One study demonstrated that higher pulse rates are associated with increased symptoms of AMS (O'Connor et al., 2004), but there was no correlation between individual changes in HR and AMS in the present study.

Even though mean MAP was not changed from preSTG to postSTG, one of the more interesting yet unexpected findings in the present study was that individual changes in AMS-C and MAP from preSTG to postSTG were significantly correlated (Fig. 3). One hypothesis regarding the resolution of AMS with altitude acclimatization involves downregulation of efferent renal sympathetic nerve activity such that the kidneys can sustain diuresis and prevent or limit the edema associated with high altitude illness (Hackett et al., 1982; Swenson, 2001; Ledderhos et al., 2002). Individual decreases or increases in MAP in the present study may be a marker of decreased or increased sympathetic activation, respectively.

## Conclusions

In conclusion, 6 d of staging at 2200 m were well tolerated, yet induced ventilatory and hematologic acclimatization such

that both the incidence and severity of AMS were greatly reduced following rapid, high-risk ascent to 4300 m. The ventilatory, cardiovascular, and hematologic adjustments at the staging altitude were relatively minor, but these adjustments ultimately conferred significant benefits during ascent to a higher altitude. Although 6 d of staging at 2200 m did not induce typical cardiovascular changes associated with altitude acclimatization, individual changes in MAP and AMS-C from preSTG to postSTG were significantly correlated. These results suggest that downregulation of the sympathetic nervous system and resultant effects on the cardiovascular and renal systems may be important physiologic adaptations during staging that reduce susceptibility to AMS during rapid, high-risk ascent to 4300 m.

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## Disclosures

Authors Beidleman, Fulco, Muza, Rock, Staab, Forte, Brothers, and Cymerman have no conflicts of interest or financial ties to disclose.

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